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RESEARCH**

APPLICATION NUMBER:

19-555/S-008

19-555/S-016

PHARMACOLOGY REVIEW

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

NDA number: 19-555

Serial number/date/type of submission: SE8-016 / 4 October 2000 / PM
SLR-008 / 27 March 2001 / BL
SE5-016 / 31 May 2001 / BZ

Information to sponsor: Yes

Sponsor and/or agent: Schering Corporation

Reviewer name: Paul C. Brown

Division name: Division of Dermatologic and Dental Drug Products

HFD #: 540

Review completion date: August 2, 2001

Drug:

Trade name: Diprolene AF Cream

Generic name (list alphabetically): betamethasone dipropionate

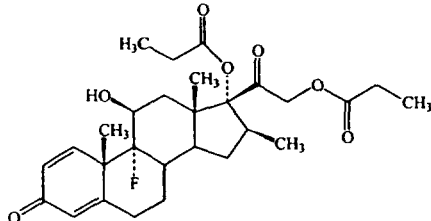
Code name: SCH11460

Chemical name: 9-fluoro-11 beta, 17, 21-trihydroxy-16 beta-methylpregna-1, 4-diene, 3, 20-dione 17, 21-dipropionate

CAS registry number: 5593-20-4

Molecular formula/molecular weight: $C_{28}H_{37}FO_7$ / MW=504.60

Structure:



Related NDAs: NDA 16-322, NDA 16-740, NDA 16-932, NDA 17-536, NDA 17-691, NDA 17-781, NDA 17-829, NDA 19-408, NDA 19-716, NDA 18-741

Drug Class: corticosteroid

Indication: Corticosteroid responsive dermatoses

Clinical formulation: 0.05% cream

Route of administration: topical

Introduction and drug history:

The sponsor has conducted several clinical studies in pediatric patients. The 10/4/00 and 5/31/01 submissions are a supplement that includes information from these studies in a revised label.

A pharm/tox review for this NDA was written, dated 8 April 1999, in which revisions to the Carcinogenesis, Mutagenesis and Impairment of Fertility section of the label were recommended. The sponsor had conducted three genotoxicity studies and submitted the reports of these studies to this and several other NDA's for betamethasone containing products. It was recommended at that time that the sponsor revise future versions of labels for products containing betamethasone to include the specific genotoxicity information about betamethasone. The label in the 3/27/01 submission contains changes in the labeling made in response to these recommendations.

Labeling review:

The Carcinogenesis, Mutagenesis, and Impairment of Fertility section of the label for this drug as proposed in the 3/27/01 submission is shown below. Deleted sections are shown as strikeout and added sections are highlighted.

Carcinogenesis, mutagenesis, and impairment of fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of betamethasone dipropionate.

Betamethasone was negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*), and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was positive in the *in-vitro* human lymphocyte chromosome aberration assay, and equivocal in the *in-vivo* mouse bone marrow micronucleus assay. This pattern of response is similar to that of dexamethasone and hydrocortisone.

The sentences used to describe the genotoxicity information are the same as those recently found acceptable for Lotrisone lotion (Letter signed 12/8/00), which is another Schering product that contains betamethasone dipropionate. These modifications to the label adequately describe the results of the studies and are acceptable from a pharm/tox perspective.

The description of the fertility studies differs from the description used in the Lotrisone label. It may be more appropriate to substitute the wording used in the Lotrisone label to be consistent and to provide a comparison of the doses used in the animal studies with the human dose.

The Pregnancy section of the label in the 3/27/01 submission from the sponsor reads as follows.

Pregnancy: Teratogenic effects: Pregnancy category C: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. This dose is approximately 26 times the human topical dose of DIPROLENE AF Cream assuming human percutaneous

absorption of approximately 3% and the use in a 70 kg person of 7 g per day. The abnormalities observed included umbilical hernias, cephalocele and cleft palate.

There are no adequate and well-controlled studies in pregnant women. DIPROLENE AF Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

This wording appears to differ from previous versions of the label for Diprolene AF Cream. In previous versions the description of the rabbit study was not included in the label. The wording of this section appears to be almost identical to the wording used for Diprolene Gel. The only difference being the substitution of AF Cream for Gel. It is not clear how the human to animal dose ratio was calculated or how the 3% absorption figure was obtained. If the 3% absorption value is for Diprolene Gel, then it may not be appropriate to use this same number for Diprolene AF Cream. This section should probably be changed to use absorption information specific to Diprolene AF Cream if such information exists. Otherwise, the dose ratio should be calculated based on the maximum possible human dose. The description of the rabbit study would read as follows if the maximum daily human dose was used for the dose comparison (see appendix for dose multiple calculations).

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. This dose is approximately 0.2 fold the maximum human dose based on a mg/m² comparison. The abnormalities observed included umbilical hernias, cephalocele and cleft palates.

In addition to this change, the following sentence has been used at the end of the Pregnancy section in Diprosone and previous Diprolene labels, but appears to have been deleted here.

Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

It may be appropriate to restore this sentence to the end of the Pregnancy section to be consistent with the other betamethasone propionate labels.

Regulatory Conclusion:

The sponsor should include the specific genotoxicity, fertility and teratogenicity information about betamethasone in the label of Diprolene AF Cream.

Recommendations:

The text for the Carcinogenesis, Mutagenesis, and Impairment of Fertility section and the Pregnancy section shown below should be used in the label for Diprolene AF Cream. This incorporates genotoxicity, fertility and teratogenicity information about betamethasone into the label and makes the label consistent with other Schering betamethasone containing products. This may be done after an overall review of the label involving all disciplines via a Division labeling meeting. (*Note: This information was incorporated into a draft label for this NDA during a labeling meeting on 8/1/01.*)

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of betamethasone dipropionate.

Betamethasone was negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*), and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was positive in the *in-vitro* human lymphocyte chromosome aberration assay, and

equivocal in the *in-vivo* mouse bone marrow micronucleus assay. This pattern of response is similar to that of dexamethasone and hydrocortisone.

Reproductive studies with betamethasone dipropionate carried out in rabbits at doses of 1.0 mg/kg by the intramuscular route and in mice up to 33 mg/kg by the intramuscular route indicated no impairment of fertility except for dose-related increases in fetal resorption rates in both species. These doses are approximately 5 and 38 fold the human dose based on a mg/m² comparison, respectively.

Pregnancy: Teratogenic effects: Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. This dose is approximately 0.2 fold the maximum human dose based on a mg/m² comparison. The abnormalities observed included umbilical hernias, cephalocele and cleft palates.

Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Paul C. Brown, Ph.D.
Reviewing Pharmacologist

cc:

NDA 19-555

HFD-540

HFD-540/Pharm/Brown

HFD-540/Sup./Jacobs

HFD-540/MO/Cook

HFD-540/Chem/Pappas

HFD-540/PM/Cintron

Draft date (# of drafts):

Concurrence Only:

HFD-540/DD/Wilkin

HFD-540/Sup./Jacobs

August 2, 2001 (1st draft)

Appendix 1: Dose multiple calculations.

Maximum human dose:

$$\frac{45 \text{ g cream/week}}{7 \text{ days/week}} = 6.4 \text{ g cream/day (assumes density of 1 g/ml)}$$

For betamethasone dipropionate:

$$6.4 \text{ g lotion/day} \times 0.0643\% = 4.1 \text{ mg betamethasone dipropionate/day}$$

$$\frac{4.1 \text{ mg/day}}{60 \text{ kg}} = 0.07 \text{ mg /kg/day (assumes 60 kg human)}$$

$$0.07 \text{ mg/kg/day} \times 37 = 2.59 \text{ mg/m}^2/\text{day} \quad (km = 37)$$

Human to animal dose comparison based on body surface area.

Dose in mg/kg	Dose in mg/m ² (mg/kg × km)	Multiple of human dose (mg/m ² ÷ 2.59 mg/m ²)
Mouse (km = 3)		
33	99	38.22
Rabbit (km = 12)		
0.05	0.6	0.23
1.0	12.0	4.63